

**What is claimed:**

1. An isolated protein comprising a light chain (LC) immunoglobulin variable domain sequence and a heavy chain (HC) immunoglobulin variable domain sequence,

wherein the LC and HC variable domain sequences form an antigen binding site with binding affinity for the human CD44 extracellular domain and wherein CDR3 of the LC variable domain sequence comprises M-Q-A-L-Q-X<sub>1</sub>-P-X<sub>2</sub>-T, where X<sub>1</sub> is threonine or absent, and X<sub>2</sub> is any amino acid or absent.

2. The protein of claim 1 wherein the LC variable domain sequence is a kappa light chain family member.

3. The protein of claim 1 wherein CDR2 of the LC variable domain sequence comprises an amino acid sequence of at least 6 amino acids of which at least 5 amino acids are identical to LGSNRAS, and

CDR1 of the LC variable domain sequence comprises an amino acid sequence of at least 15 amino acids of which at least 13 amino acids are identical to RSSQSLLHSNGYNYLD.

4. The protein of claim 3 wherein CDR2 of the HC variable domain sequence comprises: G-G-X<sub>1</sub>-T-X<sub>4</sub>-Y-A-D-S-V-K-G, where X<sub>1</sub> is hydrophobic, and X<sub>4</sub> is any amino acid.

5. The protein of claim 4 wherein each of CDR1, CDR2, and CDR3 of at least one the variable domain sequences differs by no more than two amino acid differences from a respective CDR of the HAE-A3 antibody.

6. The protein of claim 5 wherein CDR1, CDR2, and CDR3 of the HC and LC variable domain sequences are identical to respective CDRs of the HAE-A3 antibody.

7. The protein of claim 4 wherein each of CDR1, CDR2, and CDR3 of at least one the variable domain sequences differs by no more than two amino acid differences from a respective CDR of the HAE-G2 antibody.

8. The protein of claim 7 wherein CDR1, CDR2, and CDR3 of the HC and LC variable domain sequences are identical to respective CDRs of the HAE-G2 antibody.

9. The protein of claim 4 wherein each of CDR1, CDR2, and CDR3 of at least one the variable domain sequences differs by no more than two amino acid differences from a respective CDR of the HAE-H10 antibody.

10. The protein of claim 9 wherein CDR1, CDR2, and CDR3 of the HC and LC variable domain sequences are identical to respective CDRs of the HAE-H10 antibody.

11. The protein of claim 10 wherein FR3 of the HC variable domain sequence comprises: RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR.

12. The protein of claim 10 wherein FR3 of the HC variable domain sequence comprises: RFTISRDNSKNTLYLQMNSLRAEDTAVYHCAR.

13. The protein of claim 4 wherein each of CDR1, CDR2, and CDR3 of at least one the variable domain sequences differs by no more than two amino acid differences from a respective CDR of the BE-B12 antibody.

14. The protein of claim 13 wherein CDR1, CDR2, and CDR3 of the HC and LC variable domain sequences are identical to respective CDRs of the BE-B12 antibody.

15. The protein of claim 4 wherein each of CDR1, CDR2, and CDR3 of at least one the variable domain sequences differs by no more than two amino acid differences from a respective CDR of the BE-D7 antibody.

16. The protein of claim 15 wherein CDR1, CDR2, and CDR3 of the HC and LC variable domain sequences are identical to respective CDRs of the BE-D7 antibody.

17. The protein of claim 4 wherein each of CDR1, CDR2, and CDR3 of at least one the variable domain sequences differs by no more than two amino acid differences from a respective CDR of the BE-H10 antibody.

18. The protein of claim 17 wherein CDR1, CDR2, and CDR3 of the HC and LC variable domain sequences are identical to respective CDRs of the BE-H10 antibody.

19. The protein of claim 4 wherein each of CDR1, CDR2, and CDR3 of at least one the variable domain sequences differs by no more than two amino acid differences from a respective CDR of the BE-H9 antibody.

20. The protein of claim 19 wherein CDR1, CDR2, and CDR3 of the LC and HC variable domain sequences are identical to respective CDRs of the BE-H9 antibody.

21. An isolated protein comprising a light chain (LC) immunoglobulin variable domain sequence and a heavy chain (HC) immunoglobulin variable domain sequence, wherein the LC and HC variable domain sequences form an antigen binding site with affinity for the human CD44 extracellular domain, and each of CDR1, CDR2, and CDR3 of at least one the variable domain sequences by no more than two amino acid differences from a respective CDR of the HAE-B8 antibody.

22. The protein of claim 21 wherein CDR1, CDR2, and CDR3 of the LC and HC variable domain sequences are identical to respective CDRs of the HAE-B8 antibody.

23. An isolated protein comprising a light chain (LC) immunoglobulin variable domain sequence and a heavy chain (HC) immunoglobulin variable domain sequence, wherein the LC and HC variable domain sequences form an antigen binding site with affinity for the human CD44 extracellular domain, and each of CDR1, CDR2, and CDR3 of at least one the variable domain sequences by no more than two amino acid differences from a respective CDR of the HAE-F1 antibody.

24. The protein of claim 23 wherein CDR1, CDR2, and CDR3 of the LC and HC variable domain sequences are identical to respective CDRs of the HAE-F1 antibody.

25. An isolated protein comprising a light chain (LC) immunoglobulin variable domain sequence and a heavy chain (HC) immunoglobulin variable domain sequence, wherein the LC and HC variable domain sequences form an antigen binding site with affinity for the human CD44 extracellular domain, and each of CDR1, CDR2, and CDR3 of at least one the variable domain sequences by no more than two amino acid differences from a respective CDR of the BE-A11 antibody.

26. The protein of claim 25 wherein CDR1, CDR2, and CDR3 of the LC and HC variable domain sequences are identical to respective CDRs of the BE-A11 antibody.

27. A recombinant cell that contains one or more nucleic acids that encode the immunoglobulin variable domain sequences of the protein of claim 1.

28. A method of providing a CD44-binding antibody, the method comprising: providing the recombinant cell of claim 27; and maintaining the cell under conditions in which the one or more nucleic acids are expressed and the protein comprising the LC and HC immunoglobulin variable domain sequences is produced.

29. An isolated nucleic acid that comprises a first and second coding sequence, wherein the first coding sequence encodes a first immunoglobulin chain that comprises the LC variable domain sequence of the protein of claim 1, and the second coding sequence encodes second immunoglobulin chain that comprises the HC variable domain sequence of the protein.

30. A method of modulating activity of a CD44-expressing cell in a subject, the method comprising:

administering, to a mammalian subject, a composition that comprises the protein of claim 1, 21, 23, or 25, the composition being administered in an amount effective to modulate the activity of a CD44-expressing cell in the subject.

31. An isolated protein comprising a heavy chain immunoglobulin variable domain sequence and a light chain immunoglobulin variable domain sequence, wherein the protein binds to CD44 ectodomain with a  $K_d$  of less than  $2 \times 10^{-7}$  M and comprises at least two human CDRs.

32. The protein of claim 31 wherein the framework regions of the heavy and light chain variable domain are human.

33. The protein of claim 31 wherein the protein is not immunogenic in humans.

34. The protein of claim 31 wherein the protein inhibits HA binding to CD44-expressing cell KG1a cells in vitro by at least 20% inhibition at a concentration of less than 500  $\mu\text{g/mL}$ .

35. The protein of claim 34 wherein the protein inhibits HA binding to a CD44-expressing cell KG1a cells in vitro by at least 50% inhibition at a concentration of less than 100  $\mu\text{g/mL}$ .

36. A method of modulating activity of a CD44-expressing cell in a subject, the method comprising:

administering, to a mammalian subject, a composition that comprises the protein of claim 34, the composition being administered in an amount effective to modulate the activity of a CD44-expressing cell in the subject.

37. The method of claim 36 wherein the subject has, is predisposed to, or is diagnosed with an inflammatory disorder.

38. The method of claim 37 wherein the inflammatory disorder is rheumatoid arthritis, lupus, restenosis, graft v. host response, or multiple sclerosis.

39. The method of claim 36 wherein the subject has, is predisposed to, or is diagnosed with a neoplastic disorder.

40. The method of claim 39 wherein the neoplastic disorder is a malignant or metastatic cancer.

41. A method of preparing a subject for receiving exogenous cells, the method comprising:

administering, to a subject, the protein of claim 12, 13, 15, 17, 19, 21, 23, or 25, in an amount effective to sensitize NK cells in the subject to cell death.